

Department of Obstetrics and Gynecology

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Research Focus

- Laboratory for Molecular Medicine (LMM) and gynecological oncology
- Specialized obstetrics and perinatal medicine
- Clinical Trial Center (CTC) and Institute for Women's Health (IFG®)
- Gynecological endocrinology and reproductive medicine

Structure of the Department

Following an extensive structural change in the women's clinic, the three traditional pillars of the field (Gynecology, Gynecologic Oncology, Obstetrics and Perinatal Medicine and Endocrinology and Reproductive Medicine) are represented clinically and scientifically in the following **organisational** units:

- University Breast Center Frankonia (UBF),
- **Gynaecological** University Cancer Center Frankonia (GKF),
- University Perinatal Center Frankonia (UPF),
- University Center for Reproductive Medicine Frankonia (UFF)
- University Endometriosis Center Frankonia (UEF).

These centers are certified by the appropriate national and international professional societies, and by quality management.

In the clinic two W2 Professorships for Translational Gynecology and Obstetrics (Prof. Dr. Peter A. Fasching) and Experimental Reproductive Medicine (Prof. Dr. rer. nat. Ralf Dittrich) were established. Interfaces of the scientific work are provided by the Laboratory for Molecular Medicine (LMM) and the associated center for clinical studies (Study Center, Institute for Women's Health, IFG®). In total more than 40 physicians work in the hospital clinically

and scientifically. They are supported by two mathematicians, two scientists and seven study nurses.

The clinic has an approval of the European Board and College of Obstetrics and Gynecology (EBCOG) as a training clinic for the European physician.

Research

Laboratory for Molecular Medicine (LMM) and gynecological oncology

In the LMM (Leader: PD Dr. rer. nat. Reiner Strick) different research approaches are being pursued. The DNA and tissue bank has been expanded. End of 2010 more than 35,200 blood and DNA samples from patients and in cooperation with the Institute of Pathology, University of Erlangen (Head: Prof. Dr. Arndt Hartmann) more than 8,200 tissue samples of benign and malignant tumors have been stored. The research groups are members of the International Breast Cancer Associated Consortium (BCAC), which has data of more than 30,000 breast cancer patients with appropriate controls.

The cancer research in the LMM (Prof. Dr. Fasching) focused on the search for gene variations and their possible correlation with disease risk and prognosis. The latter appears also to be influenced by microRNA (miRNA). Studies of this new research approach revealed several specific miRNA deregulations in the blood of breast cancer patients using miRNA chips (Dr. Michael Schrauder, PD Dr. Strick).

The continuation of a project about the different effects of tamoxifen on endometrial and breast cells showed that the signaling pathways of AKT and mTOR in these cells were differentially activated. Especially, protein phosphatases were identified as particularly important (PD Dr. Strick, PD Dr. Pamela Strissel, PhD).

The mTOR-kinase inhibitor RAD001 is an established representative of the "targeted therapies" for breast cancer treatment with promising properties. However, it also induces AKT phosphorylation, which leads to the development of resistance. Using the breast cancer MCF7 xenograft mouse model, we could show that the combination with the anti-malaria drug chloroquine (CQ), for which we have already demonstrated breast cancer protective effects, weakened the RAD001-induced AKT phosphorylation and could abrogate the resistance mechanism in cancer cells (Dr. Christian Löhberg).

The research regarding ovarian and endometrial cancer (Prof. Dr. Fasching, Dr. Thiel) in cooperation with the Ovarian Cancer Association Consortium (OCAC) aims for the identification of cancer associated gene variations. A disease-specific locus could be identified for both malignancies in studies with more than 10,000 patients. In addition the role of 14 human endogenous retroviruses (HERV) as a risk factor and importance for cell invasion and cell-cell fusion was examined. In close cooperation with the Institute of Medical Physics Erlangen (Head: Prof. Dr. Ben Fabry) a cell invasion model was established on the basis of collagen. Initial results show that Syncytin-1 (HERV-W) and the neuron-restrictive silencer factor (NRSF) regulate tumor cell invasion in an opposite manner (PD Dr. Strick, PD Dr. Strissel).

In an analysis of endometriosis tissue samples (PD Dr. Stefan P. Renner, PD Dr. Strissel) using the chip technology over 3,900 genes were found to be significantly deregulated. Above all, muscle-regulating genes showed large differences in expression. Additional studies are planned to investigate the activation of pain.

Specialized obstetrics and perinatal medicine

The groups Special Obstetrics and Perinatal Medicine (Dr. Tamme W. Goecke) together with the LMM (PD Dr. Strick) were awarded two DFG-projects to investigate the functional role of specific envelope proteins of human endogenous retroviruses (HERV-family) in the placenta. It was shown that changes of the HERV proteins Syncytin-1, -2 and -3 significantly affected the formation of placental disorders, such as HELLP-syndrome, preeclampsia and intrauterine growth retardation (IUGR).

In close cooperation with the Clinic of Children and Adolescents (Director: Prof. Dr. Dr. h.c. Wolfgang Rascher) a continuation of studies of the role of the placenta in fetal programming took place. It was shown that in placentas of small for gestational age neonates (SGA-children), a decreased gene expression of cortisol-activating and -inactivating enzymes occurred simultaneously. In children with intrauterine growth retardation (IUGR) an inverse correlation between placental gene expression of 11-beta-hydroxysteroid dehydrogenase 2 and the growth rate in the first year of life was shown.

In a multicenter study planned with 10,000 pregnant women (Clinical Gravidity Association Trials and Evaluation Program, CGATE) over a longer period of observation possible

associations of different factors in pregnancy (including health problems, lifestyle) with the etiology of diseases in later life of the mother and child are studied (Prof. Dr. P. Fasching, Dr. T. Goecke, Dr. Florian Faschingbauer). One of the objectives of the study is the detection of valid risk factors that could constitute a basis for preventive measures. Currently, the study is in the run-in phase, in which 500 patients will be introduced. Following a fertility analysis, the design of further targets is planned.

Clinical Trial Center (CTC) and Institute for Women's Health (IFG®)

Since 2001 over 150 research projects have been carried out in the IFG®. These include clinical phase I-IV studies as well as research on new surgical techniques. The clinical studies pursue innovative approaches to the etiology, diagnosis and therapy of breast, ovarian, endometrial and cervical cancer. In addition to genetic testing and chemotherapy protocols, the current "target therapies" are examined. In line with studies, which include both curative and palliative therapies, so far 1,200 patients received a treatment.

Noteworthy for breast cancer is the Preface study (LKP: Prof. Dr. Fasching), which recruitment has ended and was carried out throughout Germany under guidance of Erlangen. A total of 3500 patients were included from more than 220 study centers. The Phase-IV study examines pharmacogenetic markers, which should predict treatment effects and side effects of aromatase inhibitors. Initial analysis of toxicity are expected 2011. In regard to genital cancers the Women's Hospital (LKP: Dr. Falk Thiel) heads the AGO-cervix-1 study. This Phase-III study (expected to end 2011) compares the chemotherapy regimens paclitaxel plus topotecan and topotecan plus cisplatin in patients with recurrent or persistent cervical cancer.

Gynecological endocrinology and reproductive medicine

The research in the University reproductive center (UBF) has included the cryo-preservation of germ cells, the physiology of movements of non-pregnant uterus and the pathology of hyperandrogenism.

In an effort to restore fertility in young cancer patients after chemotherapy and / or radiotherapy, a pregnancy after homologous endoscopic transplantation of cryo-preserved ovarian tissue was achieved for the first time in Germany.

Experiments with an *ex-vivo* uterus-model showed that seminal plasma has a high potential to trigger contractions, which could be modulated by progesterone and by estradiol. The perfusion with appropriate protectives resulted in the maintenance of contractility of the whole uterus during cryopreservation.

In one of the largest retrospective evaluations on polycystic ovary syndrome (PCOS), it could be shown that the current definition of PCOS is not suitable for identifying patients with metabolic risk factors (Prof. Dr. Andreas Müller, Prof. Dr. Ralf Dittrich, PD Dr. Susanne Cupisti, Dr. Patricia G. Oppelt).

Teaching

After the implementation of a specific functional area (2008), the upgrading of quality management (QM) was further developed (PD Dr. Wolfgang Frobenius, MME; PD Dr. Susanne Cupisti). The aim was a certification according to DIN EN ISO 9001:2008, issued by the Management Service of the TÜV Süd in October 2010 after an appropriate audit. The Erlangen Women's Hospital is hence one of the first University Clinical Institutions in Germany, which has acquired a QM-certificate specifically for teaching.

Selected Publications

Dittrich R, Mueller A, Maltaris T, Hoffmann I, Magener A, Oppelt PG, Beckmann MW (2009) Hormonal and histologic findings in human cryopreserved ovarian autografts. *Fertil Steril*, 91: 1503-6

Frobenius W, Ganslandt T, Junger J, Beckmann MW, Cupisti S (2009) Effectivity of Peer Teaching for Gynecological and Obstetrical Skills Training. *Geburtsh Frauenheilk*, 69: 848-855

Schroth W, Goetz MP, Hamann U, Fasching PA, Schmidt M, Winter S, Fritz P, Simon W, Suman VJ, Ames MM, Safgren SL, Kuffel MJ, Ulmer HU, Boländer J, Strick R, Beckmann MW, Koelbl H, Weinsilboum RM, Ingle JN, Eichelbaum M, Schwab M, Brauch H (2009) Association between CYP2D6 polymorphisms and outcomes among women with early stage breast cancer treated with tamoxifen. *JAMA*, 302: 1429-36

Bolton KL, Tyrer J, Song H, Ramus SJ, Notaridou M, Jones C, Sher T, Gentry-Maharaj A, Wozniak E, Tsai YY, Weidhaas J, Paik D, Van Den Berg DJ, Stram DO, Pearce CL, Wu AH, Brewster W, Anton-Culver H, Zogas A, Narod SA, Levine DA, Kaye SB, Brown R, Paul J, Flanagan J, Sieh W, McGuire V, Whittemore AS, Campbell I, Gore ME, Lissowska J, Yang HP, Medrek K, Gronwald J, Lubinski J, Jakubowska A, Le ND, Cook LS, Kelemen LE, Brook-Wilson A, Massuger LF,

Kiemeny LA, Aben KK, van Altena AM, Houlston R, Tomlinson I, Palmieri RT, Moorman PG, Schildkraut J, Iversen ES, Phelan C, Vierkant RA, Cunningham JM, Goode EL, Fridley BL, Kruger-Kjaer S, Blaeker J, Hogdall E, Hogdall C, Gross J, Karlan BY, Ness RB, Edwards RP, Odunsi K, Moyisch KB, Baker JA, Modugno F, Heikkinen T, Butzow R, Nevanlinna H, Leminen A, Bogdanova N, Antonenkova N, Doerk T, Hillemanns P, Dürst M, Runnebaum I, Thompson PJ, Carney ME, Goodman MT, Lurie G, Wang-Gohrke S, Hein R, Chang-Claude J, Rossing MA, Cushing-Haugen KL, Doherty J, Chen C, Rafnar T, Besenbacher S, Sulem P, Stefansson K, Birrer MJ, Terry KL, Hernandez D, Cramer DW, Vergote I, Amant F, Lambrechts D, Despierre E, Fasching PA, Beckmann MW, Thiel FC, Kici AB, Chen X, Australian Ovarian Cancer Study Group, Australian Cancer Study (Ovarian Cancer), Ovarian Cancer Association Consortium, Johnatty SE, Webb PM, Beesley J, Chanock S, Garcia-Closas M, Sellers T, Easton DF, Berchuck A, Chenevix-Trench G, Pharoah PD, Gayther SA (2010) Common variants at 19p13 are associated with susceptibility to ovarian cancer. *Nat Genet*, 42: 880-4

Goecke TW, Kici AB, Niesler B, Loehberg CR, Hammer C, Rappold G, Schanze D, Straub V, Altmann HH, Strissel P, Strick R, Beckmann MW, Fasching PA (2010) Two naturally occurring variants of the serotonin receptor gene HTR3C are associated with nausea in pregnancy. *Acta Obstet Gynecol Scand*, 89: 7-14

Ruebner M, Strissel PL, Langbein M, Fahlbusch F, Wachter DL, Faschingbauer F, Beckmann MW, Strick R (2010) Impaired cell fusion and differentiation in placenta from patients with intrauterine growth restriction correlate with reduced levels of HERV envelope genes. *J Mol Med*, 88: 1143-56

International Cooperation

Prof. Bruce Ponder, Prof. Doug Easton, Breast Cancer Consortium, Cambridge, Cambridge, UK

R. Weinsilboum, MD; L. Wang, MD; J. Ingle, MD, Mayo Clinic, Rochester, MN, USA

Prof. D. Slamon, MD, PhD, David Geffen School of Medicine, UCLA, Los Angeles, CA, USA

Meetings and International Training Courses

05.-07.02.2009: Intensivkurs-Süd für Gynäkologie Endokrinologie und Reproduktionsmedizin, München

18.03.2009: Die Frau mit Mammakarzinom 2009, Erlangen

04.07.2009-05.07.0009: Erlanger Kolposkopie 2009, Erlangen

20.-21.11.2009: IV. Bayern-Seminar 2009 für Gynäkologie und Geburtshilfe, Erlangen

17.03.2010: Update Mammakarzinom, Erlangen

20.-21.03.2010: Kolposkopie Workshop, Erlangen

10.-12.06.2010: 84. Tagung Bayerische Gesellschaft für Geburtshilfe und Frauenheilkunde, Erlangen